BIOCHEMISTRY

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The Benjamin/Cummings Publishing Company, Inc.
Redwood City, California • Fort Collins, Colorado • Menlo Park, California
Reading, Massachusetts • New York • Don Mills, Ontario • Wokingham, U.K.
Amsterdam • Bonn • Sydney • Singapore • Tokyo • Madrid • San Juan

Cover

Dimer of *trp* repressor protein, with bound tryptophan (in blue). The protein binds to DNA and regulates expression of the *trp* genes that control tryptophan biosynthesis. Crystal structure by Paul Sigler et al.; image by Jane and David Richardson.

Frontispiece

Figure 11.15a The T state of aspartate transcarbamoylase, as determined by x-ray diffraction.

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Photo Research and Permissions: Rachel Menzi
Typesetter: York Graphic Services, Inc.
Film Preparation: Color Response, Inc.

Credits for photographs appear on pages xi–xiii

Library of Congress Cataloging-in-Publication Data

Mathews, Christopher, K., 1937–
Biochemistry/Christopher K. Mathews, K. E. van Holde; illustration concepts by Audre Newman with art contributions from Irving Geis.
p. cm.
Includes bibliographical references.
ISBN 0-8053-5015-2
1. Biochemistry. I. Van Holde, K. E. (Kensal Edward), 1928–
II. Title.
[DNLM: 1. Biochemistry. QU 4 M4294b]
QP514.2.M384 1990
574.192—dc20
DNLM/DLC
for Library of Congress 89-17922
CIP

ISBN: 0-8053-5015-2

BCDEFGHIJ-VH- 93210

The Benjamin/Cummings Publishing Company
390 Bridge Parkway
Redwood City, CA 94065

fore the pancreas protects itself further by synthesizing a small protein called **pancreatic trypsin inhibitor.** This competitive inhibitor binds so tightly to the active site of trypsin that it effectively inactivates it even at very low concentration. The bonding between trypsin and its inhibitor is among the strongest noncovalent associations known in biochemistry; the equilibrium constant is about 10^{13} $(mol/L)^{-1}$, corresponding to $\Delta G^\circ = -75$ kJ/mol. Only a tiny amount of trypsin inhibitor is present—far less than can inhibit all of the potential trypsin in the pancreas. Thus, only a fraction of the trypsin generated in the duodenum is inhibited, and the rest can be activated. Since protection is limited, zymogen activation can sometimes be triggered in the pancreas—for example, if the pancreatic duct is blocked. The active enzymes then begin to digest the pancreatic tissue itself. This condition, called *acute pancreatitis,* is extremely painful and sometimes fatal.

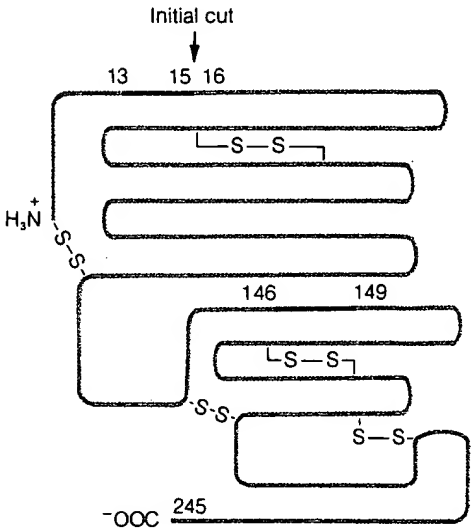

Figure 11.20
Activation of chymotrypsinogen. A schematic view of the molecule. Cleavage between amino acids 15 and 16 (arrow) results in the formation of π-chymotrypsin (green and gray regions). Subsequent removal of the segments shown in gray yields α-chymotrypsin. Note that disulfide bonds hold the structure together despite these cleavages.

Blood Clotting

Activation of zymogens is the key to another biologically important process—the clotting of vertebrate blood. If a blood clot is examined in the electron microscope, it is found to be composed of striated fibers of a protein called *fibrin* (Figure 11.21a). The fibrin monomers are elongated molecules, about 46 nm long, that stick together in an staggered array as shown in Figure 11.21b and c. The fibrin monomers are derived from a precursor, **fibrinogen,** by proteolytic cleavages that release small **fibrinopeptides.** Loss of these peptides uncovers positions at which the fibrin molecules can stick together. After the clot is formed, it is further stabilized by covalent crosslinks between glutamine and lysine residues.

The proteolysis of fibrinogen to fibrin is catalyzed by the serine protease **thrombin.** Thrombin has sequence and structural similarities to trypsin, but, as a protease with a very specific function, it cleaves only a few types of bonds, mainly (Arg–Gly). Thrombin itself is produced from **prothrombin** by another specific protease; in fact, as Figure 11.22 shows, there is a whole cascade of proteolytic activation reactions that lead ultimately to the formation of a fibrin clot. Involved are a series of proteases referred to as *factors.* In damaged tissues, the proteins **kininogen** and **kallikrein** activate factor XII (also called **Hageman factor**), which in turn activates factor XI—and the cascade of reactions proceeds as shown. This is called the **intrinsic pathway.** Alternatively, damage to blood vessels leads to the release of **tissue factor** and activation of factor VII, starting the **extrinsic pathway.** The two pathways merge in the activation of factor X, which will proteolyze and thereby activate prothrombin.

Some of the activation steps require auxiliary proteins. For example, activation of factor X in the intrinsic pathway by factor IX (**Christmas factor**) requires a 330-kDa protein called **antihemophilic factor** (factor VIII). It is the partial or complete absence of factor VIII activity that is the cause of classic **hemophilia.** The gene for factor VIII is carried on the X chromosome, so women, who have two copies of this chromosome, can be heterozygous carriers of the trait but will exhibit the symptoms only if they are homozygous. However, a male descendent who receives on his single X chromosome the damaged copy of the factor VIII gene will experience more or less severe difficulty in blood clotting. The condition can now be treated by frequent transfusions of a blood serum fraction concentrated in factor VIII. The gene for this protein has recently been cloned and expressed in

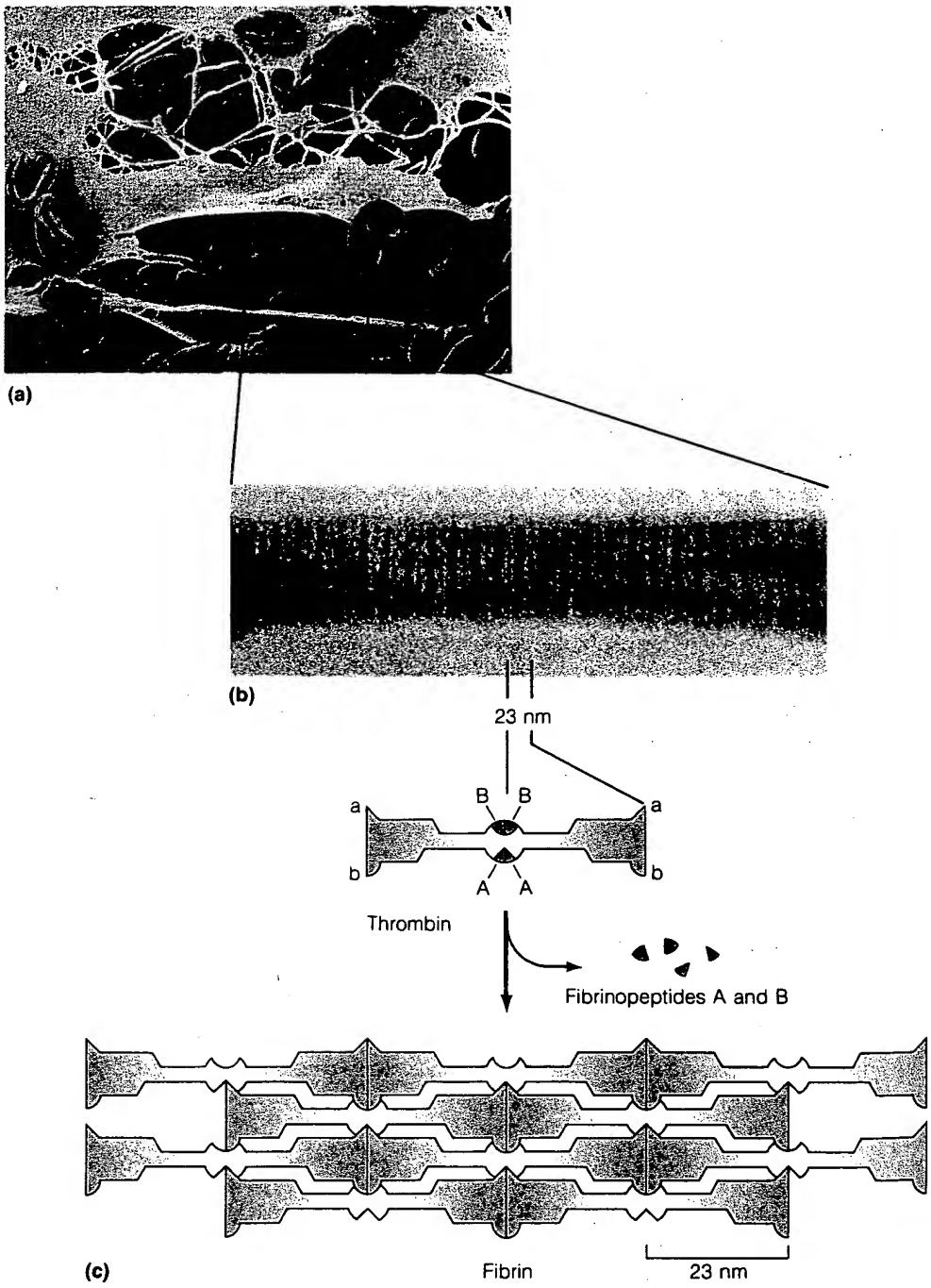

Figure 11.21
Formation of a blood clot. (a) Red blood cells enmeshed in the insoluble strands of a fibrin clot. (b) Electron micrograph of part of a fibrin fiber. (c) Schematic view of how fibrin monomers are thought to associate to form a clot fiber. Removal of fibrinopeptides A and B from fibrinogen by thrombin makes sites accessible for association with complementary sites a and b on adjacent monomers. The molecules are believed to overlap as shown, since the spacing seen in the fibers (see b above) is 23 nm—exactly half the length of the fibrinogen molecule.

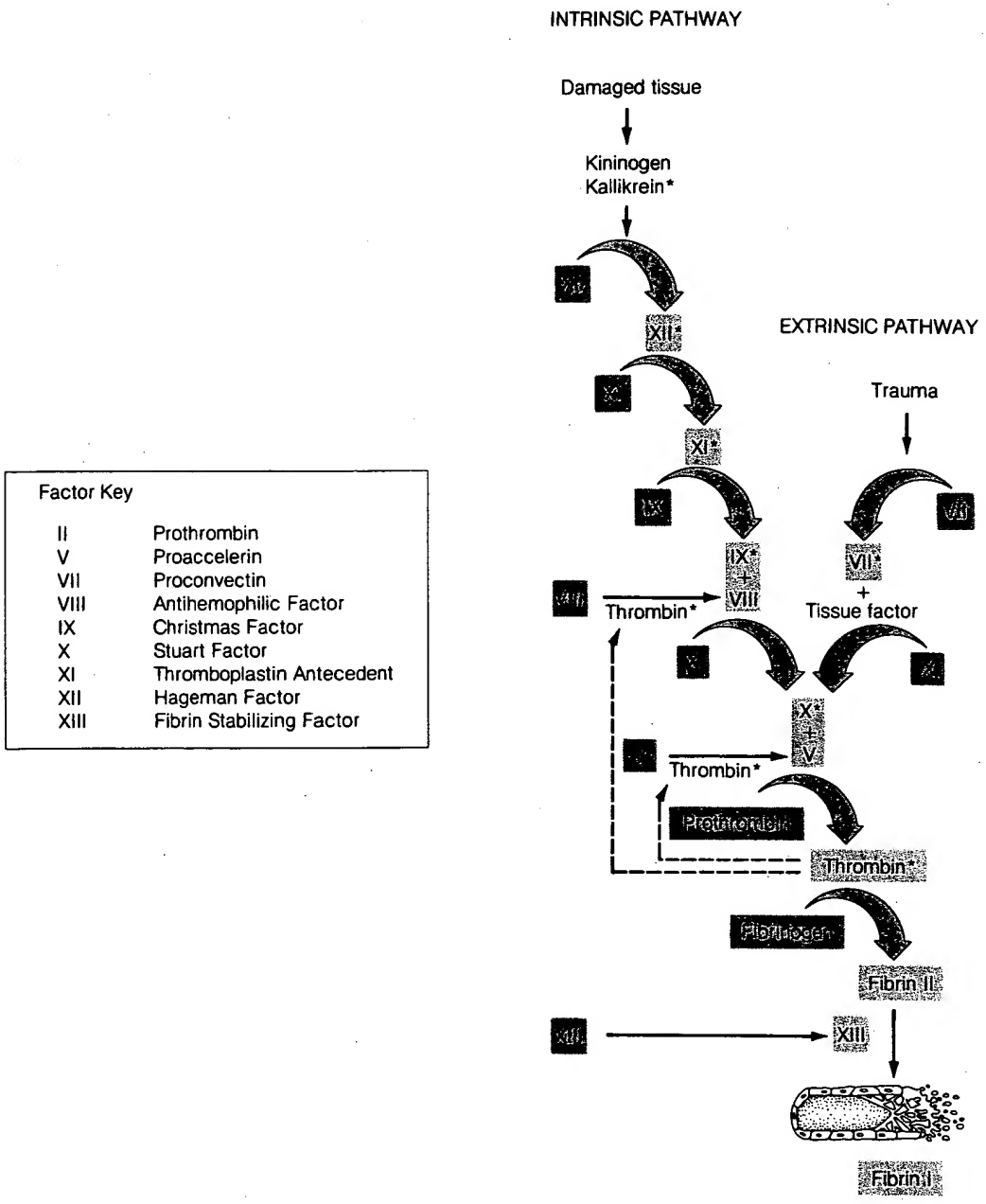

Figure 11.22
The cascade process in blood clotting. Each factor in the pathway can exist in an inactive form (red) or an active form (green). The cascade of proteolytic activations can start from exposure of blood at damaged tissue surfaces (intrinsic pathway) or from internal trauma to blood vessels (extrinsic pathway). The common result is activation of fibrinogen to clotting fibrin. Auxiliary factors that aid some steps are also shown. Asterisk (*) denotes serine proteases.

bacteria, and the availability of this synthetic factor VIII may allow such patients to avoid the dangers of regular transfusions.

Regulation by Control of Enzyme Synthesis and Degradation

All the forms of enzyme regulation we have described so far have one feature in common: they modify the activity of enzymes that are already present in the cell or tissue. Organisms have still another way in which enzymatic activity can be regulated: they can control the *synthesis* and *degradation* of specific enzymes in response to changing needs.